Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

The foregoing amendments are believed to place the claims in condition for allowance or in better condition for consideration on appeal. No new claims have been added. Various claims have been amended. The amendments do not present new issues or require additional search. 37 C.F.R. § 1.116(a). Accordingly, their entry after final rejection is respectfully requested.

Upon entry of the foregoing amendment, claims 30-34, 65, 66, 68, 74, 82-95, 186, 188, 190, 206-212, and 287-307 are pending in the application, with claims 30, 31, 65, 186, 287, 288, and 289 being the independent claims.

Claims 66 and 188 have been amended to address the Examiner's rejection under 37 C.F.R. § 1.75. Support for amendments to Claims 66 and 188 can be found at paragraphs [0016], [0021], and [0031] in the Specification. Claims 68 and 190 have been amended to address the Examiner's rejection under 35 U.S.C. § 103 by reflecting the Applicants' unexpected results as described below. Support for amendments to Claims 68 and 190 can be found in the Specification at paragraphs [0317] and [0321] and Figures 10 and 11.

Claims 287-307 were withdrawn from consideration by the Examiner in the Office Action dated January 25, 2011, as being directed to a non-elected invention.

Claims 67 and 189 have been cancelled in response to the Examiner's rejection under 37 C.F.R. § 1.75.

II. The Rejections

A. Rejection Under 35 U.S.C. § 103

Claims 30-34, 65-68, 74, 82-95, 186, 188-190, and 206-212 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Umaña *et al.* (WO 99/54342), Grabenhorst *et al., Journal of Biological Chemistry* 274:36107-36116 (1999) and Shields *et al., Journal of Biological Chemistry* 277:26733-26740 (2002) in view of Russell *et al.* (WO 01/29242 A2) and Rabouille *et al., Journal of Cell Science* 108:1617-1627 (1995). Applicants respectfully traverse this rejection as it may be applied to pending claims.

1. Declaration by Pablo Umaña

On page 4 of the Office Action dated January 25, 2011, the Examiner states the following:

> [A]pplicants' unsupported assertions that there is no reasonable expectation of success when combining the references are less than convincing in light of the reasoning provided by the Examiner and the extensive teachings provided by the prior art of record. "Argument of counsel cannot take the place of evidence lacking in the record." In re Scarbrough, 182 USPQ 298, 302 (CCPA 1974).

The Applicants' direct the Examiner to the Declaration of Pablo Umaña (unsigned) filed under 37 C.F.R. § 1.132 filed concurrently with the Amendments and Reply. A signed Declaration of Pablo Umaña will be forwarded shortly. In this Declaration, Dr. Umaña, who is the lead inventor in U.S. Appl. No. 10/761,435 and PCT Publ. No. WO 99/54342 (Umaña *et al.*), explains in detail why a skilled scientist at the time this application was filed would not have been motivated to generate the claimed fusion polypeptides and would not have had a reasonable expectation of successfully enhancing antibody Fc-receptor binding and effector function using the claimed fusion polypeptides.

First, Dr. Umaña states that both the present application and the post-filing publication Ferrara *et al.*, *Biotech. Bioeng.93*:851-861 (2006) disclose beneficial results which would be unexpected by a skilled scientist based upon the references cited by the Examiner. Second, Dr. Umaña expresses his opinion that the Examiner is incorrect in his assessment that the Applicants' claimed invention is a simple and obvious alternative to a hypothetical fusion polypeptide containing a Gal T catalytic domain and an α2,6-sialyltransferase localization domain as described in Umaña *et al.* Third, Dr. Umaña expresses his opinion that the references cited by the Examiner do not overcome the deficiencies of Umaña *et al.* in disclosing the distinct elements of the claimed invention and do not render the claimed invention obvious to try. Fourth, Dr. Umaña describes alternative strategies, many of which are disclosed by the cited references, that could be implemented by a skilled scientist in their attempt to enhance antibody function by glycoengineering technologies. Dr. Umaña states that the references cited by the Examiner do not provide evidence suggesting that the Applicants' glycoengineering strategy would successfully produce antibodies with increased ADCC, nor do the cited references provide evidence suggesting that the Applicants' strategy would be superior to these alternative strategies.

Based upon the arguments disclosed in the Declaration of Pablo Umaña and those listed below, it is respectfully requested that the rejection of pending claims 30-34, 65, 66, 68, 74, 82-95, 186, 188, 190, and 206-212 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

2. *Elements of a Prima Facie Case of Obviousness*

In order to establish a *prima facie* case of obviousness, (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (3) there must be a reasonable expectation of success that the claimed invention is achieved. MPEP § 2143. The Examiner has the burden of establishing a *prima facie* case of obviousness on all three grounds.

A. *Cited References Do Not Teach or Suggest All of the Claim Limitations*

Umaña *et al.* does not teach the use of host cells expressing fusion glycosyltransferases comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III or the methods for producing polypeptides modified by fusion glycosyltransferases comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III. Therefore, this reference does not teach all of the claim limitations. Moreover, the pending claims are not a simple and obvious alternative to the teachings of Umaña *et al.*

In making the argument that the pending claims are obvious to try in light of Umaña *et al.*, the Examiner stated the following:

> Umana et al suggest that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the trans Golgi network, e.g. α2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII substrates.

See page 6 of the Office Action dated January 21, 2010. This argument is addressed in detail on pages 4-6 of the Declaration by Pablo Umaña. In his Declaration, Dr. Umaña states that the Examiner is incorrect in his assessment of this cited reference as it relates to the Applicants' claimed invention.

To summarize the arguments made by Dr. Umaña in his Declaration relating to this issue, Dr. Umaña states that Umaña *et al.* teaches away from the Applicants' claimed glycoengineering strategy in two aspects. First, Umaña *et al.* teaches the enhancement of antibody ADCC by multiple strategies involving the alteration of glycosyltransferase co-substrates. As an example, Umaña *et al.* teaches the genetic manipulation of the sugar nucleotide transport into the Golgi as a means to enhance the ADCC of target antibodies. *See* WO 99/54342 at page 39, lines 4-19. Second, the fusion glycosyltransferases claimed by the Applicants would yield different glycosylation profiles from the hypothetical fusion glycosyltransferase disclosed by Umaña *et al.*, because differing enzymatic activities are being relocalized. Furthermore, the direction of relocalization in the Applicants' claimed glycoengineering strategy (directionally from trans to cis) is opposite to that proposed by Umaña *et al.* Dr. Umaña also explains that the glycoengineering strategy disclosed by the Applicants and the hypothetical strategy disclosed in Umaña *et al.* differ in their intended effects on the glycosylation profile of the target polypeptide. Based upon these arguments, Umaña *et al.* does not render Applicants' claims obvious, because this reference teaches several strategies lacking the distinct elements of Applicants' claims and having different intended outcomes associated with said strategies.

Grabenhorst *et al.* involves mapping the donor glycosyltransferases within the Golgi/trans-Golgi network. This reference does not teach or suggest the specific elements of the claimed invention, glycoengineering of antibodies for enhanced Fc-receptor binding or effector function, and does not discuss the redistribution of GnT III within the Golgi network. Grabenhorst *et al.* do not discuss the creation of fusion glycosyltransferases containing the GnT III glycosyltransferase domain and the Golgi localization domain of a Golgi resident polypeptide other than GnT III or any fusion glycosyltransferase containing a Man II Golgi localization domain. Rather, Grabenhorst *et al.* describes a fusion peptide containing the FT-6 glycosylation domain as a reporter enzyme and the GnT III localization domain. Therefore, Grabenhorst *et al.* does not cure the aforementioned deficiency of Umaña *et al.* in disclosing all of the claim limitations. Neither reference alone nor the combined references suggest that increased ADCC would result from Applicants' claimed methods, as further detailed in Section B.

Shields *et al.* reports the use of a fucosylation-deficient CHO cell line variant (Lec 13) to produce an IgG1 polypeptide with increased FcγRIII affinity. This reference does not disclose any information relating to GnT III glycosyltransferase activity or the effects of glycosyltransferase relocalization on antibody effector function. Shields *et al.* does not provide experimental data related to glycoengineering in any capacity, nor does it teach the glycoengineering of polypeptides with fusion glycosyltransferases containing glycosylation and localization domains from different Golgi resident polypeptides. Rather, Shields *et al.* is limited in scope to characterizing ADCC of non-fucosylated antibodies produced from a preexisting cell line and does not indicate the biochemical origin of the cell line's inability to add fucose to IgG1. The only recommendation

concerning glycoengineering of antibodies mentioned in Shields *et al.* is the treatment of fucosylated IgG with fucosidases. In this capacity, Shields *et al.* teaches away from the pending claims. In summary, Shields *et al.* does not cure the aforementioned deficiencies of Umaña *et al.* and Grabenhorst *et al.* in teaching or suggesting all of the claim limitations.

B. No Reasonable Expectation of Success When Combining the Cited References

The teachings of Umaña *et al.* do not provide a reasonable expectation of success to one of ordinary skill in the art for enhancing antibody effector functions by modifying antibody glycosylation with a fusion glycosyltransferase comprising a GnT III glycosyltransferase domain and the Golgi localization domain of a Golgi resident polypeptide other than GnT III, because this reference teaches away from the pending claims as mentioned above in the following manner: (A) the pending claims involve relocalization of a different glycosyltransferase than Gal T proposed by Umaña *et al.*, and the direction of relocalization (*i.e.* trans to cis) within the Golgi is opposite to that proposed by Umaña *et al.* and (B) Umaña *et al.* teach away from the pending claims by suggesting the manipulation of glycosylation co-substrates. Despite differences in the strategies of Umaña *et al.* and in the specific goals of said strategies as compared to the pending claims, Umaña *et al.* only indicates that it ***might*** be desirable to redistribute the Gal T glycosyltransferase towards the TGN instead of the trans-Golgi cisterna. At most, this constitutes an invitation to experiment and does not provide the requisite reasonable expectation for successfully producing or modifying the glycosylation profile of

antibodies having increased Fc-receptor binding or effector function by the use of fusion glycosyltransferases as recited in the specification and pending claims.

Nor does Grabenhorst *et al.* provide any reasonable expectation of successfully practicing the pending claims, because this reference does not disclose the use of fusion glycosyltransferases with GnT III glycosyltransferase activity. Furthermore, this reference does not deal with antibody glycosylation. If one of ordinary skill in the art were to combine the teachings of Umaña *et al.* and Grabenhorst *et al.*, the combined art would give no indication as to which of many possible choices is likely to be successful in regards to the effects of GnT III relocalization on antibody glycosylation and ultimately antibody effector function. Since Shields *et al.* is limited in scope to characterizing fucose-deficient antibodies produced by a cell line and does not address the effect of GnT III on antibody glycosylation, this reference does not limit the scope of possible choices likely to be successful in achieving Applicants' claimed invention. In summary, the cited references do not provide a reasonable expectation of success, because the cited references teach away from Applicants' claims and fail to provide the requisite direction as to which of many possible choices is likely to be successful. As discussed on page 7 of the Declaration of Pablo Umaña, the Applicants' claimed invention was the product of data obtained through experimentation rather than a product of assembled previously disclosed knowledge.

3. Impermissible Hindsight Leads to Picking and Choosing

The Examiner has declared that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

While the Applicants have indeed addressed the Examiner's rejections by discussing the combination of cited references, the Applicants nevertheless assert that addressing the shortcomings of the cited references individually is also critically important in establishing that each cited reference cannot cure the deficiencies of the references in combination. Arguing each reference individually enables the Applicants to refute the underpinnings of an Examiner's argument based on hindsight reconstruction. Quoting *Ex parte Frye*, "An appellant may attempt to overcome an Examiner's obviousness rejection on appeal to the Board by submitting arguments and/or evidence to show that the Examiner made an error in either (1) an underlying finding of fact upon which the final conclusion of obviousness was based, or (2) the reasoning used to reach the legal conclusion of obviousness." *Ex parte Frye*, App. 2009-006013 (Bd. App. Feb. 26, 2010) (precedential). The Applicants assert that arguing (1) "just the facts" is a lower hurdle than arguing against (2) the Examiner's reasoning.

The Applicants submit that the Examiner has erred in the obviousness rejection by using the claimed invention as a framework to pick out each element of Applicants' novel glycoengineering strategy from the cited references and reconstruct the pending claims. Quoting *Ex parte Haymond*,

> We note that it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together isolated disclosures and teachings of the that a [103 rejection] must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. He may not, because he doubts the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217 (Bd. App. 1996) citing with approval *In re Warner*, 379 F.2d 1011 (CCPA 1967) cert. denied 389 U.S. 1057 (1968).

Grabenhorst *et al.* does not deal with the problem addressed by the Applicants, *i.e.* improving antibody function, and Shields *et al.* and Grabenhorst *et al.* do not teach any of the specific limitations of the pending claims. The totality of the prior art does not offer focused and specific teachings towards the proposed claims, and both Shields *et al.* and Umaña *et al.* teach away from Applicants' glycoengineering strategy and claims. Rather than demonstrate that concrete examples of each claim limitation exists in the cited references, the Examiner has constructed a scenario of how the patentee would have arrived at his strategy. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir., 1984) explains that an Examiner is not entitled to use a claim as a "frame" and to employ "[i]ndividual naked parts of separate prior art references... as a mosaic to recreate a facsimile of the claimed invention."

4. Russell and Rabouille

Concerning Russell and Rabouille, the Applicants maintain that while Russell purportedly discusses the use of Golgi localization domains to redistribute glycosyltransferases in the plant Golgi pathway and Rabouille purportedly discusses the distribution of GnT I and Man II in the Golgi, neither reference teaches the use of fusion polypeptides having GnT III activity and comprising the Golgi localization domain of a Golgi resident polypeptide other than GnT III to produce modified polypeptides having increased Fc-receptor binding or effector function in mammalian cells. Additionally, the references combined fail to provide a reasonable expectation for successfully using the recited fusion glycosyltransferases in mammalian host cells to produce modified polypeptides having increased Fc-receptor binding or effector function.

5. *Evidence of the Unexpected Superior Results of the Presently Claimed Methods Rebuts Any Prima Facie Case of Obviousness*

As explained on pages 3, 4 and 7 in the Declaration of Pablo Umaña, experimentation yielded unexpected superior results which could not be predicted by one of ordinary skill in the art at the time of the Application's filing. For example, cells expressing the Man II-GnT III fusion glycosyltransferase (Fig. 4) produced a higher proportion of antibodies associated with increased ADCC in comparison to cells expressing the GnT I-GnT III fusion polypeptide (Fig. 3), which in turn was superior to cells expressing the WT-GnT III fusion polypeptide (Fig. 2). *See* specification at page 98, paragraph 255. This result is unexpected, because GnT I and Man II have similar spatial distributions, i.e. co-distribute, within the Golgi sub-compartments. *See* specification at page 98, paragraph 255. Based on the teachings of the references, a person of ordinary skill in the art at most would expect the glycosylation profiles resulting from the glycosyltransferase activity of the Man II-GnT III and the GnT I-GnT III fusion glycosyltransferases to be similar. The use of a Man II localization domain in a fusion glycosyltransferase containing GnT III activity is embodied in claims 68 and 190, which are currently amended to reflect this unexpected result.

In view of the discussion provided above, Applicants would again like to direct the Examiner's attention to the unexpected superior results described in their post-filing publication, Ferrara *et al., Biotech. Bioeng. 93*:851-861 (2006) ("Ferrara"). As described in the Applicants' Reply dated January 21, 2010, the unexpected superior results presented in Ferrara provide further support of the unexpected superior results also disclosed in the present Specification in Figures 4, 11, 29, and 31. For example, Figure 4

of the Specification discloses that in comparison to a fusion glycosyltransferase with GnT III activity and a GnT I localization domain, a fusion glycosyltransferase with GnT III activity and a Man II localization domain exhibited more efficient production of antibodies associated with enhanced ADCC. As stated above, these unexpected superior results cannot be predicted by the teachings of the cited references due to co-distribution of GnT I and Man II within the Golgi. These findings are supported by Figure 4 and pages 856-857 of Ferrara, which show that overexpression of GnT III in mammalian host cells co-expressing antibodies led to production of antibodies with lower FcγRIIIa binding affinity as compared to antibodies that had been glycoengineered in host cells co-expressing fusion glycosyltransferases comprising rat GnT III catalytic domains and human Man II Golgi localization domains. Figure 5A of Ferrara shows that antibodies modified by fusion glycosyltransferases having rat GnT III catalytic activity and human Man II Golgi localization domains have superior ADCC as compared to unmodified antibodies.

6. Summary

The Examiner asserts that the combination of Umaña, Grabenhorst, Shields, Russell, and Rabouille references renders the claims obvious. As explained above, the claimed methods are non-obvious, because the cited references (1) do not provide grounds for a *prima facie* case of obviousness, (2) are used as a mosaic to recreate a facsimile of the claimed invention, and (3) could neither predict the outcome of expression of the claimed fusion glycosyltransferases on polypeptide glycosylation and function nor the disclosed unexpected and beneficial results. Based upon the arguments herein and those disclosed in the Declaration of Pablo Umaña, it is respectfully requested

that the rejection of pending claims 30-34, 65, 66, 68, 74, 82-95, 186, 188, 190, and 206-212 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

B. Rejection Under 37 CFR 1.75 – Double Patenting

The Examiner advised the applicants that should claim 65 be found allowable, claims 66 and 67 will be objected to under 37 C.F.R. 1.75 as being a substantial duplicate thereof. The examiner further advised the applicants that should claim 186 be found allowable, claims 188 and 189 will be objected to under 37 C.F.R. 1.75 as being a substantial duplicate thereof. Claims 67 and 189 have been cancelled. In regards to claims 66 and 188, we respectfully disagree with the examiner. Dependent claims 66 and 188 are narrower in scope to their respective independent claims 65 and 186. We have amended claim 66 and 188 to include "[t]he Golgi localization domain of a Golgi resident polypeptide other than β(1,4)-N-acetylglucosaminyltransferase III." The independent claims 65 and 186 describe a fusion polypeptide having β(1,4)-N-acetylglucosaminyltransferase III ***activity***, whereas their respective dependent claims 66 and 188 are limited to a fusion polypeptide ***consisting essentially of*** the ***catalytic domain*** of β(1,4)-N-acetylglucosaminyltransferase III and the Golgi localization domain of a Golgi resident polypeptide other than β(1,4)-N-acetylglucosaminyltransferase III. We respectfully request the Examiner to reconsider the objection to claims 66 and 188 under 37 C.F.R. 1.75.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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